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Hepatitis C Virus Infection and Lymphoproliferative Diseases in France: A National Study

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The putative role of hepatitis C virus (HCV) infection in the pathophysiology of lymphoproliferative diseases (LPD) is supported by North American and southern European studies reporting high HCV seroprevalence in patients with B-cell-non-Hodgkin lymphoma (NHL). In order to evaluate the situation in France, we conducted a retrospective national study about the association of chronic HCV infection and LPD. 72 Internal Medicine and Infectious Diseases departments were contacted. Response rate was 51.4%. We recorded 43 LPD (19 males, 24 females): 31 B-cell-NHL, 4 Waldenström's macroglobulinemia, 3 chronic lymphocytic leukemia, 2 multiple myeloma, 2 lymphomas of the mucosa-associated lymphoid tissue, and 1 Hodgkin's disease. Mean age at HCV diagnosis was 62 years (range 33–84). In 16 cases, LPD occurred in patients known to be HCV-infected. For 11 patients, LPD diagnosis preceded the diagnosis of HCV infection, whereas diagnosis was done simultaneously in 11 patients. For those with accurate infection date, mean interval between both events was 15.2 years. Fourteen patients had HCV extrahepatic manifestations: 9 mixed cryoglobulinemia, including 7 with NHL, 5 sicca syndrome (5 NHL), and both in one patient. Cohort of HCV-infected patients could be accurately determined for 16 departments, totaling 1,485 patients and 37 cases. Thus, from our data the frequency of LPD among HCV-infected patients approximates 2.49%. Despite possible bias inherent to this retrospective study, our data support the hypothesis of HCV-associated LPD and particularly B-cell-NHL. In France, this association is much lower than in Italy. Further studies are needed to assess the precise role of HCV in the multistep process leading to monoclonal proliferation. Am. J. Hematol. 64:107–111, 2000.

Key words: hepatitis C virus; non-Hodgkin's lymphoma; mixed cryoglobulinemia; sicca syndrome; lymphoproliferative diseases

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INTRODUCTION

The putative role of hepatitis C virus (HCV) infection in the pathophysiology of lymphoproliferative diseases (LPD) is still controversial. Discordant data have been reported by North American, southern European, and northern European authors about the frequency of HCV infection in patients with non-Hodgkin lymphoma [1–16]. Recently, French authors reported no association [17]. We conducted a national multicenter retrospective study to precise the situation in France.

MATERIALS AND METHODS

In 1995, French internists and infectious diseases physicians were contacted to form a research and study group on HCV infection named GERMIVIC (Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le virus de l'hépatite C). Physicians were recruited in general hospitals and university hospitals. To evaluate the association between HCV infection and LPD, we conducted a national survey-based retrospective study. Each member of the GERMIVIC group was questioned about any case of hemopathy in his cohort of patients infected with HCV. For each case, a chart was completed including age, sex, human immunodeficiency virus (HIV) status, HCV infection history including extrahepatic manifestations, type of hemopathy, and, if available, time between both diagnoses.

RESULTS

Type and Distribution of Hemopathy

Among 72 Internal Medicine and Infectious Diseases departments contacted, 37 gave an answer (reponse rate: 51.4%). Twenty-eight departments reported at least one case of LPD (75.7%), whereas 9 departments denied following patient with both HCV infection and hemopathy. A total of 63 hemopathies were recorded in 63 patients. Because LPD in HIV-infected subjects exhibit distinctive features and complex pathophysiology, we excluded the 20 HIV-patients for further analysis. The distribution of the 43 remaining hemopathies in patients seronegative for HIV is shown in Table I. There were 31 B-cell non-Hodgkin-lymphoma (NHL), 3 chronic lymphocytic leukemia, 4 Waldenström's macroglobulinemia, 2 multiple myeloma, 2 lymphomas of the mucosa-associated lymphoid tissue (MALT lymphoma), and 1 Hodgkin's disease.

TABLE I. Distribution of the 43 Lymphoproliferative Disorders in HCV-Infected Patients

Hemopathy	Number (percentage)
B-cell NHL[a]	31 (72%)
Waldenström's macroglobulinemia	4 (9.3%)
Chronic lymphocytic leukemia	3 (7%)
MALT lymphoma	2 (4.7%)
Multiple myeloma	2 (4.7%)
Hodgkin's disease	1 (2.3%)

[a]NHL, non-Hodgkin's lymphoma; MALT, mucosa-associated lymphoid tissue.

HCV Infection Characteristics

Mean age at HCV infection diagnosis was 62 years (range 33–84). There were 19 males and 24 females. Sixteen departments among 22 reporting non-HIV-infected cases could accurately estimate their population of HCV-infected patients, for a total of 1,485 subjects. Thirty-seven cases of LPD came from these departments. Thus, from our data we estimated the frequency of hemopathy among HCV-infected patients to be 2.49% (37/1,485).

Time relationship between HCV infection and hemopathy is shown in Table II. In 11 cases (29%) diagnosis of LPD preceded the diagnosis of HCV infection (mean interval: 7.9 years; range 2–27). In 16 cases (42%) hemopathy occurred in patients known to be HCV-infected (mean duration between both events: 4 years). Diagnosis was done simultaneously in 11 patients (29%). Data were not available in 5 cases.

Because HCV genotype was not available in most patients, no correlation between genotype and LPD occurrence could be determined.

The route of transmission was unknown in 21 patients (49%), whereas 22 patients reported blood product transfusion (51%). For those 22 patients, the period of infection could be accurately determined. Mean duration between contamination and HCV infection diagnosis was 15.2 years. There was no intravenous drug abuser. Fourteen patients had HCV extrahepatic manifestations: 9 symptomatic mixed cryoglobulinemia including 7 with NHL, 5 sicca syndrome (5 NHL), and both in one. Another patient, with no history of interferon therapy, had autoimmune thyroiditis. Twenty patients (54%) received interferon α therapy in association with ribavirin in 3 patients, and 17 had no anti-HCV treatment. Data concerning antiviral therapy were not available in 6 patients.

DISCUSSION

The putative role of chronic HCV infection in the pathophysiology of LPD has been only recently elicited. Most often, authors have conducted retrospective studies focusing on HCV seroprevalence in cohort of patients with LPD. Controversial data have been published depending on geographical origin of patients. Italian authors reported a strong association between HCV and LPD with seroprevalence ranging from 9 to 34% in NHL [1–8]. HCV seroprevalence in control groups—including

TABLE II. Main Characteristics of the 43 HCV-Infected Patients With LPD

Mean age (years)	62 (33–84)
Sex ratio	
Male	19
Female	24
Time relationship between LPD diagnosis and HCV diagnosis[a]	
LPD before HCV	
Number of patients	11
Mean interval (years)	7.9
LPD after HCV	
Number of patients	16
Mean interval (years)	4
Simultaneously	11
Not available	5
HCV route of transmission	
Unknown	21
Blood product transfusion	22
Intravenous drug abuse	0

[a]LPD, lymphoproliferative disease; HCV, hepatitis C virus.

patients with non-B LPD, other hematological malignancies or blood donor cohorts—ranged from 0 to 5.4%. Although North American and Japanese authors found similar results [9–11], northern European publications reported 0–1% HCV seroprevalence in NHL, thus controverting a possible association [12–17]. Previous published HCV seroprevalence data are summarized in Table III. In order to evaluate the situation in France, we had a different approach. We conducted a national survey-based retrospective study of LPD in HCV patients. From our data, the frequency of LPD in HCV-infected patients approximates 2.5%. Because return rate on the questionnaire was about 50%, we cannot exclude self-selection in that mainly those centers with LPD patients may have responded. In Italy, Ferri et al. reported 14 cases of NHL in a cohort of 500 chronically HCV infected patients, thus giving a similar rate of 2.8% [18].

Mean age of our patients was similar to that of NHL in French population [19], i.e., 63 for male and 65 for female, and in accordance with Italian data [5,7,18]. Age consideration is important for data comparison. It has been postulated that if chronic HCV-mediated stimulation of B cells could predispose to NHL, a long duration of HCV infection could be necessary to induce clinically evident clonal proliferation [12,20–22]. This concept may explain the low HCV seroprevalence reported in younger patients with NHL [15].

In the present study, among all types of LPD, B-cell-NHL accounted for two-thirds of cases. Multiple myeloma and Hodgkin's disease were uncommon. This distribution is in accordance with previous studies showing the preferential association of HCV infection with B-cell-NHL [1,3–5,7,8,16; Table IV). Our series includes 2 cases of MALT lymphoma which is an infrequent type of LPD. Pioltelli et al. reported a 36.4% HCV seroprevalence in MALT lymphoma [1], but this has not been confirmed by French authors who found a 2.2% seroprevalence among 46 gastric MALT lymphoma [22].

In the majority of our patients, HCV infection preceded LPD with a mean delay of 4 years between both diagnoses. This argues for the putative role of HCV in the multistep process leading to LPD [21]. However, duration of infection before hemopathy diagnosis is uncertain because infection date cannot always be accurately determined, except in the group of blood product receivers. In this group, mean interval between infection and LPD diagnosis was 15.2 years. In 11 patients of our series, diagnosis of LPD preceded HCV serology determination. However we cannot exclude prior long-term asymptomatic HCV infection before serologic testing.

In the group of 22 blood product receivers, transfusion preceded LPD diagnosis in all but 3 patients. The relatively high HCV seroprevalence reported in LPD might result from the frequency of blood product administration during hemopathy management. However, previous studies did not show significant association between history of transfusion during LPD and HCV seroprevalence [4,7,11,23].

Hepatitis C virus has been involved in the pathogenesis of extrahepatic manifestations such as mixed cryoglobulinemia and sicca syndrome [19,25–28]. Because NHL may complicate the course of both disorders, it is not surprising that previous studies found higher HCV prevalence in patients with B-cell-NHL and mixed cryoglobulinemia [2,5,8,16,29]. We report similar results in that 7/9 patients with symptomatic mixed cryoglobulinemia had NHL. Moreover, the LPD type in all 5 patients with sicca syndrome was B-cell-NHL. HCV is a hepatotropic as well as lymphotropic virus. Recently, Italian authors reported a striking prevalence of monoclonal gammopathies in patients with HCV-related chronic liver disease [30]. Both mixed cryoglobulinemia and sicca syndrome are associated with monoclonal or polyclonal B-cell expansion. Thus, in the course of chronic HCV infection, both manifestations may represent an indicator for HCV lymphotropism and/or an intermediate step in lymphomagenesis [21].

CONCLUSION

In a French national retrospective study we found that the frequency of LPD in chronically HCV-infected patients approximates 2.5%, with a striking predominance of B-cell NHL. If association between HCV and LPD does exist, this association is much lower in France than in other European countries. Because of possible bias inherent to such studies, in particular low physicians response rate and absence of control population, prospective studies with matched HCV negative control group are needed to increase our knowledge about lymphoma-

TABLE III. Previously Published Data About HCV Seroprevalence in Cohort of Patients With B-Cell-Non-Hodgkin's Lymphoma (NHL)

Country	NHL (no. of patients)	HCV prevalence in patients with NHL (%)	Controls (no. of patients)	HCV prevalence in controls (%)	Authors (ref.)
U.S.A.	120	22	No hemopathy (114)	5	Zuckerman (10)
U.S.A.	312	11.5	NA[b]	NA	Kashyap (23)
Italy	50	34	Hodgkin's disease (30)	3	Ferri (4)
			Age-matched healthy subjects (30)	1.3	
Italy	199	28.6	General population (6917)	2.87	Mazzaro (5)
Italy	126	0–50[a]	Blood donors (832)	1	Pioltelli (1)
			Elderly population (94)	8.9–10.5[a]	
Italy	115	32	Healthy controls (70)	0	Zignego (2)
Italy	24	33	Healthy controls (30)	0	Ferri (3)
Italy	91	23	Blood donors (1568)	1.9	De Rosa (7)
Italy	311	9	NA	NA	Silvestri (8)
Japan	54	22.2	NA	NA	Izumi (9)
Canada	100	0	Nonhematological malignancies (100)	0	Collier (24)
France	201	2	Hodgkin's disease (94)	1.1	Germanidis (17)
U.K.	38	0	NA	NA	Hanley (12)
Scotland	35	0	NA	NA	McColl (13)
Scotland	72	0	NA	NA	McColl (14)
The Netherlands	115	0	NA	NA	Thalen (15)
Total	1963	14.1			

[a]HCV seroprevalence showed a positive linear trend with age group.
[b]NA, not available.

TABLE IV. Previously Published Data About HCV Seroprevalence in Miscellaneous Hematologic Disorders[a]

Country	LPD (no. of patients)	HCV prevalence (%)	Authors (ref.)
U.S.A.	Non-B-cell hemopathy (268)	4.5	Zuckerman (10)
Italy	Hodgkin's disease (30)	3	Ferri (4)
Italy	Other hem. malign. (153)	3.1	Mazzaro (5)
Italy	Hodgkin's disease (78)	0–14.8[b]	Pioltelli (1)
Italy	Hodgkin's disease (50)	8	Zignego (2)
Italy	Hodgkin's disease (20)	0	Ferri (3)
Italy	MGUS (48)	22.9	
	CLL (48)	16.7	
	MM (56)	16	De Rosa (7)
	Hodgkin's disease (43)	2.3	
	T-cell-NHL (9)	0	
Italy	MM (78)	4	
	T-cell-NHL (57)	4	Silvestri (8)
	ALL (23)	4	
	Hodgkin's disease (68)	0	
Japan	Non B-cell NHL (20)	0	Izumi (9)
	Hodgkin's disease (9)	0	
France	MALT (46)	2.2	Tkoub (22)
U.K.	MM (24)	0	Hanley (12)
	MGUS (10)	0	
Scotland	CLL (35)	0	McColl (13)
Scotland	CLL (38)	0	McColl (14)

[a]NHL, non-Hodgkin's lymphoma; HCV, hepatitis C virus; MM, multiple myeloma; CLL, B-cell chronic lymphocytic leukemia; MGUS, monoclonal gammapathy of uncertain significance; MALT, lymphoma of the mucosa-associated lymphoid tissue; ALL, acute lymphoblastic leukemia; Hem. malign., hematological malignancy.
[b]HCV seroprevalence showed a positive linear trend with age group.

genesis and its cofactors. HCV is a worldwide emerging chronic infection. Epidemiological data reported by several countries show a considerable increase of NHL incidence in the last two decades [31,32]. The putative role of HCV and place of type II mixed cryoglobulinemia in the multistep process leading to clonal B-cell expansion has to be thoroughly determined.

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